Vasorelaxation in Space

Peter Norsk, Morten Damgaard, Lonnie Petersen, Mikkel Gybel, Bettina Pump, Anders Gabrielsen, Niels Juel Christensen

Abstract—During everyday life, gravity constantly stresses the cardiovascular system in upright humans by diminishing venous return. This decreases cardiac output and induces systemic vasoconstriction to prevent blood pressure from falling. We therefore tested the hypothesis that entering weightlessness leads to a prompt increase in cardiac output and to systemic vasodilatation and that these effects persist for at least a week of weightlessness in space. Cardiac output and mean arterial pressure were measured in 8 healthy humans during acute 20-s periods of weightlessness in parabolic airplane flights and on the seventh and eighth day of weightlessness in 4 astronauts in space. The seated 1-G position acted as reference. Entering weightlessness promptly increased cardiac output by 29±7%, from 6.6±0.7 to 8.4±0.9 L min⁻¹ (mean±SEM; P=0.003), whereas mean arterial pressure and heart rate were unaffected. Thus, systemic vascular resistance decreased by 24±4% (P=0.017). After a week of weightlessness in space, cardiac output was increased by 22±8% from 5.1±0.3 to 6.1±0.1 L min⁻¹ (P=0.021), with mean arterial pressure and heart rate being unchanged so that systemic vascular resistance was decreased by 14±9% (P=0.047). In conclusion, entering weightlessness promptly increases cardiac output and dilates the systemic circulation. This vasorelaxation persists for at least a week into spaceflight. Thus, it is probably healthy for the human cardiovascular system to fly in space. (Hypertension. 2006; 47:69-73.)

Key Words: blood pressure ■ cardiac output ■ cardiovascular diseases ■ heart rate ■ vascular resistance

Throughout evolution of mankind, gravity has constantly stressed the cardiovascular system by diminishing venous return of blood to the heart.¹ This gravity-induced decrease in venous return, and thus in cardiac output, is detected by cardiopulmonary and arterial baroreflexes, which initiate constriction of the vasculature to prevent blood pressure from falling. Therefore, gravity is a chronic systemic vasoconstrictor in upright humans during normal everyday life.

Previous cardiovascular measurements in astronauts in space indicate that cardiac output is increased by some 18% by weightlessness compared with upright standing or sitting on the ground and more so during the initial days of flight than at the end.² ³ In these studies, blood pressure was not measured. In another study, Fritsch-Yelle et al⁴ observed in 12 astronauts over several flights that the mean 24-hour diastolic arterial pressure, but not systolic pressure, was significantly decreased in space by some 5 mm Hg. This decrease was evident at the beginning and at the end of flight. However, cardiac output was not measured. Therefore, it is not known whether the unchanged systolic and decreased diastolic pressure in space is accounted for by systemic vasodilatation and whether systemic vasodilatation is evident from the very beginning and to the end of flight.

We therefore tested the hypothesis that the weightlessness-induced increase in cardiac output leads to systemic vasodilatation from the very beginning and to the end of a week in space to prevent blood pressure from increasing. Cardiac output and mean arterial pressure were, on 1 occasion, measured in subjects during very acute weightlessness of only 20-s duration in parabolic airplane flights and on another occasion in astronauts on the seventh and eighth day of spaceflight on board the space shuttle Columbia (STS-107). In this way, we explored whether the human circulation is chronically dilated by weightlessness during at least a week of spaceflight, which would indicate that it is healthy for the cardiovascular system to fly in space.

Methods

Study Design
Cardiac output, heart rate, and blood pressure were measured in 8 healthy subjects (35 years of age [range 20 to 53 years]; weight 75 kg [range 48 to 101 kg]; height 174 cm [range 160 to 191 cm]; and male/female ratio 4:4) during 20 s of weightlessness in parabolic airplane flights organized by the European Space Agency (ESA) in Bordeaux, France. To explore the more chronic effects of weightlessness, the same cardiovascular measurements by same methodology were conducted in a separate group of 4 healthy astronauts (45 years of age [range 41 to 48 years]; weight 77 kg [range 68 to 93 kg];
Each parabolic flight campaign lasted 3 days. On each day, 30 parabolic maneuvers were conducted during a 2.5-hour flight in an A300 Airbus. The parabolic maneuver included a pull-up phase for 20 s, with the Gs gradually increasing to 1.8 followed by a prompt 0-G phase for 20 s. This was followed by a pull-out phase, during which the G-level suddenly attained 1.8 and thereafter gradually decreased to 1 over 20 s. There were 2 to 8 minutes in between each maneuver, during which the reference 1-G control measurements were conducted with the subjects in seated (n=8) or supine (n=6) positions. The measurements were performed 1 to 3× in each subject with regard to each G-level and body position and thereafter averaged. Ambient temperature varied between 20°C and 23°C and humidity between 3% and 35% at a cabin pressure of 850 millibars.

During the STS-107 space mission, the same measurements were conducted on the seventh and eighth days of flight after overnight sleep and 1.5 hours after intake of a standardized breakfast. The in-flight measurements were obtained in each subject 3 to 4× over a 3-hour period at 1- or 2-hour intervals. The spaceflight data were compared with similar measurements on the ground 8 months before flight at Johnson Space Center in Houston, Texas, also after overnight sleep and 1.5 hours after intake of same standardized breakfast. On the ground, the measurements were performed on 1 day with the subjects in the seated position, and on the following day, with the subjects supine or vice versa (sequence randomized). These positions were maintained from 1.5 hours before the first measurement and until the study was completed. The data were averaged. Ambient temperature varied between 25°C and 27°C with humidity between 3% and 35% at a cabin pressure of 850 millibars.

Acute weightlessness during the parabolic flights increased seated cardiac output by 29%±7%, from 6.6±0.7 to 8.4±0.9 L min⁻¹ (P<0.003) without increasing mean arterial pressure (95±5 and 91±6 mm Hg). Therefore, systemic vascular resistance decreased by 24%±4%, from 15.3±1.2 to 11.5±1.1 mm Hg L⁻¹ min (P=0.017; Figure 1). Heart rate was unchanged by weightlessness (82±7 and 84±7 bpm).

Compared with the horizontal supine position (n=6), weightlessness increased cardiac output from 7.5±0.9 to

Cardiac Output and Functional Residual Capacity
Cardiac output was measured by noninvasive rebreathing equipment (Advanced Respiratory Monitoring System or Innocor; Innovision A/S) developed for spaceflight by ESA and described in detail previously. The subjects rebreathed through a mouthpiece back and forth into a bag with 1.4 to 1.8 L (30% of vital capacity) of a gas mixture consisting of 0.5% N₂O or 1.6% freon-22 (blood-soluble tracer gases), 0.1% to 1% SF₆ (nonblood-soluble tracer gas), and 25% to 28% O₂ in N₂. The disappearance rate of N₂O or freon-22 from the rebreathing air into blood was calculated from end-expiratory concentrations measured by a photoacoustic and magnetoacoustic multigas analyzer connected through a tube to the mouth piece. Based on the blood solubility coefficients (Bunsen) of these gasses, the disappearance rates were used for calculation of pulmonary capillary blood flow, which is equal to cardiac output. End-expiratory concentrations of SF₆ were used to correct for inadequate mixing of air in lungs with gas mixture from the rebreathing bag and for changes in rebreathing volume. Rebreathing lasted 30 s with a rate of 20 minutes⁻¹.

Functional residual capacity, which is the amount of air in the lungs after a normal expiration (37°C, ambient pressure, and saturated with water vapor), was calculated as the distribution space of SF₆ during rebreathing minus the volume of gas mixture in the rebreathing bag before rebreathing.

During the parabolic flights, rebreathing was commenced 10 s before entering 0 G, and the variables were only calculated from the end-expiratory gas concentrations during the 0-G period.

Blood Pressure and Heart Rate
Blood pressure and heart rate were measured in conjunction with rebreathing by an infrared photoplethysmographic technique (Pertapress) in an index finger or, with regard to 2 subjects during parabolic flights, by an oscillometric technique in an upper arm (Propaq 102). The hydrostatic reference level for the blood pressure measurements at 1 G was chosen at the fourth intercostal space, when the subjects were seated, and at the midaxillary line, when they were supine.

Data Analysis
Systemic vascular resistance was calculated by dividing mean arterial pressure with cardiac output. An ANOVA for repeated measures, followed by a post hoc multiple range test (Newman–Keuls), was used for detection of statistical significant differences (P<0.05) between the means of each variable during: (1) weightlessness, (2) the 1-G seated position, and (3) the 1-G supine position. If not otherwise indicated, the effects of weightlessness are related to those of the 1-G seated position because awake humans are normally upright.

Ethics
All subjects gave their written informed consent to participate, and the protocols were approved by the NASA institutional review board, the ESA medical board, and the French ethics committee of the Bordeaux area.

Results
Acute Weightlessness
Acute weightlessness during the parabolic flights increased seated cardiac output by 29%±7%, from 6.6±0.7 to 8.4±0.9 L min⁻¹ (P<0.003) without increasing mean arterial pressure (95±5 and 91±6 mm Hg). Therefore, systemic vascular resistance decreased by 24%±4%, from 15.3±1.2 to 11.5±1.1 mm Hg L⁻¹ min (P=0.017; Figure 1). Heart rate was unchanged by weightlessness (82±7 and 84±7 bpm).

Compared with the horizontal supine position (n=6), weightlessness increased cardiac output from 7.5±0.9 to

Figure 1. A, Cardiac output (L min⁻¹) measured by a rebreathing technique. B, Systemic vascular resistance (SVR) calculated by dividing mean arterial pressure with cardiac output (mm Hg L⁻¹min). The 3 columns represent means±SE of n=8, when they were 1-G supine (SUPINE; n=6), 1-G seated (SEAT), and weightlessness for 20 s (0 G) during parabolic flights in an A300 Airbus. *Statistical significant difference (P<0.05) between indicated columns.
8.8±1.1 L min⁻¹ (P=0.023; Figure 1). Thus, even the transverse gravitational load in supine subjects compresses the chest, which apparently has an inhibitory effect on the blood supply to the heart.

**Chronic Weightlessness**

During 6 to 7 days of spaceflight, the cardiovascular system adapted to a level, which was very similar to that of acute weightlessness during parabolic flights. Thus, cardiac output was increased by 22±8%, from 5.1±0.3 (seated) to 6.1±0.1 L min⁻¹ in weightlessness (P=0.021), whereas mean arterial pressure and heart rate were unchanged (82±2 and 84±4 mm Hg and 69±4 and 68±9 bpm, respectively). Thus, systemic vascular resistance was decreased by 14±9%, from 16.2±0.6 to 13.7±0.8 mm Hg L⁻¹ min (P=0.047; Figure 2).

Functional residual capacity was 2.7±0.2 L in space and thus unchanged compared with when seated on the ground (2.9±0.2 L) but increased compared with that of supine (2.2±0.1 L; P=0.015). Compared with the horizontal supine position, cardiac output in space tended to be less and systemic vascular resistance elevated (Figure 2).

**Discussion**

Compared with the ground-based upright posture, our data show that cardiac output is increased and the vasculature dilated and relaxed from the very onset of weightlessness and until at least a week into spaceflight. Systemic vasodilatation is most probably accounted for by chronic stimulation of blood pressure reflexes to prevent blood pressure from increasing. That central blood volume is expanded in space is indicated by the chronic increase in cardiac output and is supported by previous echocardiographic indications that weightlessness distends the heart chambers.⁶–⁸

Because functional residual capacity is increased in space compared with that of the ground-based supine position, the increase in cardiac output is not only accomplished by the lack of pull of gravity on the blood column but also by expansion of the lungs and thoracic cage. Expansion of the lungs and thoracic cage creates a negative pressure around the heart and central vessels, which increases venous return and thus cardiac output. That this is the case is indicated by previous results from our group that esophageal pressure, which reflects changes in interpleural pressure, decreases more by acute weightlessness than central venous pressure does when referring to the 1-G supine position.⁸ Thus, central transmural venous pressure increases. This is probably the reason that Buckey et al⁶ observed a decrease in central venous pressure shortly into spaceflight despite the fact that the heart chambers were expanded. Such a condition, in which cardiac output is elevated and the lungs and thoracic cage simultaneously expanded, cannot be simulated on the ground. Thus, the lung–heart interaction is unique in weightlessness and important for maintaining cardiac output increased during prolonged spaceflight.

Our observation that systemic vascular resistance decreased in space might at first glance seem contradictory to observations by Watenpaugh et al,⁹ who reported that calf vascular resistance doubled after 4 to 12 days of spaceflight. However, these investigators used the ground-based supine position as reference. Therefore, their observations are in accordance with ours that systemic vascular resistance tended to increase in space compared with when the subjects were ground-based supine (Figure 2). However, this increase was much less than the doubling in calf vascular resistance observed by Watenpaugh et al.⁹ Therefore, it is likely that there are regional differences in the human circulation during spaceflight concerning degree of vasodilatation or constriction.

That cardiac output is increased and the circulation chronically dilated throughout a week in space is in contrast to the previously observed high levels of sympathetic nervous activity and renin-angiotensin-aldosterone during spaceflight.¹⁰–¹² Such activations of vasoconstrictor hormones usually reflect that the vasculature is constricted and central blood volume reduced. This was clearly not the case in this study. Therefore, whether the vascular sensitivity to sympathetic nervous activity and renin-angiotensin is reduced by weightlessness should be investigated in the future.

By comparing the data in Figure 1 with those in Figure 2, it is clear that the cardiovascular changes were attenuated throughout a week in space compared with the immediate 20-s responses. This attenuation over time could have been caused by a reduction in blood volume and by a smaller cardiac muscle mass.¹³,¹⁴ It is noteworthy that cardiac output and systemic vascular resistance after a week in weightlessness adapt to a level in between that of the ground-based seated and horizontal supine positions (Figure 2). This is similar as to how renal responses to saline and water loadings adapt to spaceflight.¹⁰,¹¹ This level of adaptation in between supine and upright might constitute the natural operating
Possible Limitations

By using the foreign gas rebreathing method, we measured the pulmonary capillary blood flow of oxygenated blood, which is similar to cardiac output, when there is no significant physiological shunting of the blood in the lungs. Therefore, if different degrees of physiological shunting of blood had been present during the ground-based and in-flight conditions, this could have impacted our determinations of cardiac output. However, we have, in a previous study, observed that only when the arterial oxygen saturation is \(<95\%\) can it lead to significant underestimations of cardiac output.\(^{15}\) It is not likely that this was the case in our healthy astronauts.

Because of the peripheral location in the finger of our blood pressure measurements, it could be argued that local vasoconstriction could have led to erroneous estimations of mean arterial pressure. However, we evaluated the continuous arterial pressure curves carefully for such artifacts. Another argument for error is that location of the hydrostatic reference point at the fourth intercostal space for the arterial pressure measurements was not correct. Location of the hydrostatic reference point is crucial when comparing ground-based measurements with those during weightlessness because in this latter condition, all hydrostatic pressure gradients are abolished. We chose the fourth intercostal space as the hydrostatic reference point during the upright 1-G conditions because it is near to mid-heart level, at which brachial blood pressure is usually measured by the standard clinical methods.

Conclusion

Entering weightlessness induces prompt cardiac distension with an increase in cardiac output. The increase in cardiac output induces a baroreflex-mediated systemic vasodilatation to prevent blood pressure from increasing. These effects last for at least a week in space and indicate that weightlessness relaxes the circulation in humans. Therefore, long-term missions such as those for 6 months on the International Space Station might in fact be healthy for the cardiovascular system of astronauts. It is also of interest that the increase in cardiac output in space is not only accomplished by abolishment of hydrostatic pressure gradients but also by chronic expansion of the lungs and thoracic cage, which creates a negative pressure around the heart and central vessels and thus augments cardiac filling. Therefore, the lung–heart interaction plays a unique role as to how the heart and central circulation adapts to prolonged weightlessness.

Perspectives

On the ground, humans are normally upright with a higher hydrostatic pressure in the lower than in the upper parts of the body. This increase in hydrostatic pressure induces vasoconstriction and structural thickening of the vessel walls of the dependent arteries.\(^{16}\) Vasoconstriction and thickening of vessel walls predispose to hypertension. Therefore, during everyday life, the chronic effects of gravity might contribute to development of hypertension and cardiovascular disease.

Our data indicate that it is healthy for the circulation in astronauts to fly in space because the systemic circulation is chronically dilated and the hydrostatic pressure in the dependent portions of the body abolished. If the systemic circulation is maintained dilated for spaceflights lasting more than a week, long-term weightlessness could be healthy for the cardiovascular system in astronauts. This should be investigated in the near future on board the International Space Station, where astronauts currently fly for up to 6 months.

Whether it is healthy or not for the human heart per se to fly in space is, however, not clear at present. Martin et al\(^ {17}\) observed that immediately after 129 to 144 days of spaceflight, left ventricular ejection fraction was decreased, whereas left ventricular end-systolic volume was increased. This indicates that cardiac contractility is compromised by long-term weightlessness, which does not seem to be healthy for the heart. In contrast to this, Atkov et al\(^ {18}\) concluded from results of ultrasound examinations in 15 cosmonauts after 2.5 to 8 months of spaceflight that left ventricular end-systolic volume decreased and ejection fraction increased. Therefore, the results of Atkov et al\(^ {18}\) do not indicate that long-term weightlessness compromises cardiac contractility. In a ground-based preflight and postflight investigation, Perhonen et al\(^ {19}\) observed that after spaceflight of only 10-day duration, left ventricular muscle mass as estimated by nuclear magnetic resonance decreased by 12%, suggesting that even short durations of stays in weightlessness induces cardiac muscle atrophy. However, this has very recently been challenged by Summers et al,\(^ {20}\) who, by using echocardiography within a few hours after landing, observed a reduction in left ventricular muscle mass of 9% after 9 to 16 days of spaceflight, but that this reduction already disappeared 3 days thereafter. Thus, these authors suggested that the decrease in left ventricular muscle mass was not caused by cardiac muscle atrophy but was a mere consequence of the well-known loss in extracellular fluid during spaceflight, which had reduced the cardiac interstitial space. Therefore, whether it is healthy or not for the heart to fly in space is today not clear, and addressing this issue should be given a high priority for future missions.

Our data also have implications for understanding how gravity stresses patients with heart failure. Heart failure is characterized by a high sensitivity to the pull of gravity because the pumping capacity of the heart is reduced. Therefore, the vasculature is constricted to prevent blood pressure from falling. To alleviate the stress of gravity in compensated heart failure, we previously immersed heart failure patients into thermoneutral water (34.5°C). Compared with the upright seated control position, water immersion increased stroke volume index and decreased vascular resistance.\(^ {20,21}\) Thus, the circulatory condition in the heart failure patients improved. Because our results presented here from parabolic flights and spaceflight are in compliance with those of water immersion,\(^ {20,21}\) it is fair to conclude that gravity is a constant burden for heart failure patients and that it aggravates their condition. Therefore, a future purpose should be to...
investigate how to alleviate gravitational stress in heart failure.

Acknowledgments

This research was supported by Danish Research Agency grant 2006-01-0012. This work is dedicated to the seven heroic crew members of the fatal STS-107 flight on board the space shuttle Columbia in 2003, to whom we are eternally grateful. They never returned to Earth. Without their perseverance and ingenuity, the results would not have been obtained. We are also indebted to the staff people at ESA, ESTEC, and at NASA, Johnson Space Center, for excellent support.

References

Vasorelaxation in Space

Peter Norsk, Morten Damgaard, Lonnie Petersen, Mikkel Gybel, Bettina Pump, Anders Gabrielsen and Niels Juel Christensen

Hypertension. 2006;47:69-73; originally published online November 21, 2005;
doi: 10.1161/01.HYP.0000194332.98674.57

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/47/1/69

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/